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EXAMINER	
DAVIS, MINH TAM B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,226	BOSCH, MARNIX L	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/09/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of claims 1-32, species: 1) dendritic cells isolated from peripheral blood, 2) BCG and Interferon gamma as the dendritic maturing agent, and 3) CD86 as the co-stimulatory molecule, in the reply filed on 08/20/07 is acknowledged.

The traversal is on the ground(s) that the species share a common function for the following reasons:

1) Maturation agents do not all share the same chemical structure, but do share the common functional feature of being capable of inducing immature dendritic cells to mature. The agents identified by the Examiner as species (2) comprise a number of dendritic cell maturation agents that are known to the skilled artisan.

2) Partially mature dendritic cells can be distinguished from immature dendritic cells by an increase in expression of any one of three cell surface co- stimulatory molecules, CD80, CD86 and/or CD54. The Examiner has also required election of one of these three molecules as species (3). As the expression of the c-stimulatory molecules is induced by any of the maturation agents, election of only one of the co-stimulatory molecules is not understood.

This is not found persuasive because of the following reasons:

1) The different maturing agents do not share the same structure, or the same function. They have different structure and produce different stages of maturation of DCs, and different DCs having different properties (see Labeur et al, 1999, J Immunol, 162: 168-175, and US 20050059151 by Bosch et al)

2) CD80, CD86 and/or CD54 do not share the same structure or function.

The requirement is still deemed proper and is therefore made FINAL.

In a telephonic conversation with the Attorney Brian Poor on 10/04/07, Applicant was informed with claims 10-12 have been withdrawn from consideration as being drawn to non-elected species.

Accordingly, claims 1-9, 13-32, species: 1) BCG and interferon gamma, or LPS, TNF-alpha as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule are examined in the instant application.

The species dendritic cells obtained from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood has been rejoined with the species dendritic cells obtained from peripheral blood, the species LPS and TNF-alpha have been rejoined with the species BCG and interferon gamma, and the species CD80 has been rejoined with the species CD86, because these species have been found in the art.

The species: 1) maturation agent, which is an imidazoquinoline compound, a synthetic double stranded polyribonucleotide, a agonist of a Toll-like receptor (TLR), a sequence of nucleic acids containing unmethylated CpG motifs known to induce the maturation of DC, or any combination thereof, and 2) co-stimulatory agent CD54 have been withdrawn from consideration, as being drawn to non-elected species.

Claim Rejections - 35 USC § 112, First Paragraph, Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 13-20, 27-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) a method for producing an anti-cancer immune response in an individual with a cancer and 2) a composition comprising dendritic cells treated with BCG and interferon gamma, for administering into a cancer tissue, cancer bed, tissue area surrounding the cancer tissue, into a lymph node directly draining into a cancer area, or directly to a circulatory vessel duct that delivers blood or lymph to the cancer or a cancer afflicted organ, or into the circulatory system such that the cells are delivered to the cancer or cancer afflicted organ, wherein said dendritic cells can take up and process antigen and are enabled to induce an anti-cancer immune response subsequent to administration to the cancer tissue, does not reasonably provide enablement for: 1) a method for producing an anti-"**tumor**" immune response in an individual with a "tumor" and 2) a composition comprising dendritic cells treated with BCG and interferon gamma, for administering into the "tumor", tumor bed, tissue area surrounding the tumor tissue, into a lymph node directly draining into a tumor area, or directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, wherein said dendritic cells can take up and process antigen and are enabled to induce an anti-cancer immune response subsequent to administration to the tumor tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A tumor encompasses any enlargement or abnormal growth, which is not necessarily cancerous, for example, cystic of the pancreas, splenic tumor or enlargement of the spleen, etc... (Stedman's medical dictionary, 25th ed, 1990, p.1652-1653).

It is not clear how one can successfully assess cancer therapy, wherein the cells to be assessed are tumor cells, which are not necessarily cancerous, and are unrelated to cancer, and thus having different etiology and characteristics, and would not predictably response to cancer therapy.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly claimed.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Labeur et al, 1999, J Immunol, 162: 168-175.

Claims 1-2, 5 are as follows:

1. (Original) A method for producing an anti-tumor immune response comprising administration to an individual with a tumor a cell population comprising dendritic cells that have been partially matured in vitro, wherein the partially matured dendritic cells can take up and process antigen and are enabled to induce an anti-tumor immune response subsequent to administration to the individual.

2. (Original) The method according to claim 1, wherein the dendritic cells are obtained from bone marrow.

5. (Original) The method according to claim 1, wherein the dendritic cells are partially matured in the presence of a dendritic cell maturation agent.

It is noted that in claim 1, the ability to take up and process antigen **does not have to be subsequent** to administration to the individual.

Labeur et al teach that different culture conditions produce **dendritic cells** (DCs) with different degree of maturation, and capacity to **present antigen after incubation with the antigen** (abstract, p 168, second column, second and third paragraphs, bridging p.169, p.171, second column, paragraph under Allostimulatory activity and presentation of OVA peptide, and fig. 3 on page 172). It is noted that the ability to present antigen after being exposed to the antigen is the same as the ability to uptake and process antigen. Labeur et al teach that administration of the DCs induce protective **tumor immunity** in mice (p.172, and figure 5 on page 174).

The method taught by Labeur et al is the same as the claimed method, using the same dendritic cells, which can take up and process antigen, and induce an anti-tumor immune response when administered into an individual, and which are not terminally differentiated mature (Labeur et al, p.2 last line, bridging p.3), i.e. partially mature.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, supra, in view of Murphy et al (US 5,788,963, filed on 07/31/1995).

Claims 2-4 are as follows:

2. (Original) The method according to claim 1, wherein the dendritic cells are obtained from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, or peripheral blood.

3. (Original) The method according to claim 2, wherein the dendritic cells are obtained from the individual to be treated.

4. (Original) The method according to claim 2, wherein the dendritic cells are obtained from a healthy individual HLA-matched to the individual to be treated.

The teaching of Labeur et al has been set forth above.

Labeur et al do not teach that: 1) DCs are obtained from skin, spleen, thymus, lymph nodes, umbilical cord blood, or peripheral blood, and 2) DCs are obtained from the individual to be treated or from a healthy individual HLA-matched to the individual to be treated.

Murphy et al teach isolation of DCs for prostate cancer therapy, where DCs are obtained from any tissue where they reside, including **the skin, the spleen, bone marrow, lymph nodes and thymus** as well as the circulatory system, including blood and lymphs (column 5, lines 54-65). Murphy et al teach that human **peripheral blood** is an easily accessible ready source of human DCs (column 5, lines 59-60). Murphy et al teach that **cord blood** is another source of human DCs, where a male is born into a family known to be high risk of prostate cancer, and that said DCs can be cryopreserved for later use (column 5, lines 62-65). Murphy et al teach that DCs can be obtained from prostate cancer **patient to be treated, or from healthy individual with matched HLA** in terms of HLA antigens, because patients previously treated radiation or chemotherapy often are not able to provide sufficient or effecient DCs (column 6, lines 37-57). Murphy et al teach that CD8+ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule (column 2, second paragraph). It is noted that DCs are antigen presenting cells.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to obtain the DCs taught by Labeur et al from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, or peripheral blood, as taught by Murphy et al, to increase the number of available sources for making DCs.

It would have been obvious that the DCs taught by Labeur et al have been isolated from the individual to be treated, as suggested by Murphy et all, to avoid unwanted rejection of foreign DCs. It would have been obvious that the DCs taught by Labeur et al have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al,

to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

2. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07).

Claims 6-9 are as follows:

6. (Original) The method according to claim 5, wherein the dendritic cell maturation agent is Bacillus Calmette-Guerin (BCG), interferon gamma (IFN-gamma), lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-alpha), or any combination thereof.

7. (Original) The method according to claim 6, wherein BCG comprises whole BCG, cell wall constituents of BCG, BCG-derived lipoarabidomannans, or BCG components.

8. (Original) The method according to claim 6, wherein the BCG is heat- inactivated BCG or formalin-treated BCG.

9. (Original) The method according to claim 6, wherein the effective amount of BCG is about 10^5 to 10^7 cfu per milliliter of tissue culture media and the effective amount of IFN-gamma is about 100 to about 1000 Units per milliliter of tissue culture media.

The teaching of Labeur et al has been set forth above. Labeur et al further teach that the ability of DCs matured with CD40L to promote antitumor immunity correlates with their high

efficiency of stimulating resting T cells and high production of IL-12 (p.173, second column, second paragraph). Labeur et al teach that although they do not know yet whether high efficiency of stimulating resting T cells and high production of IL-12 are responsible for their potent in vivo immunostimulatory capacity, they speculate that the IL-12 production by DCs is critical for their in vivo function, since in other system IL-12 is shown to generate a polizarization to the immune response toward the Th1 pathway in vivo, and IL-12 is also a potent inducer of IFN-gamma and TNF-alpha production by both NK cells and T cells, which cytokines are critically involved in the development of immune response (p.173, second column, second paragraph). Labeur et al teach that pulsed 2 x 10^4 DCs are injected s.c. into naïve recipient mice (p.170, first column, second paragraph). The amount of DCs taught by Labeur et al are within the range of the claimed amounts of DCs in claim 23.

Although Labeur et al teach the use of TNF-alpha, LPS and CD40L for maturing DCs (p.4, first paragraph), Labeur et al do not teach the use of BCG and interferon gamma for maturing CDs. Further, Labeur et al do not teach: 1) BCG comprises whole BCG, cell wall constituents of BCG, BCG-derived lipoarabidomannans, or BCG components, 2) the BCG is heat- inactivated BCG or formalin-treated BCG, and 3) the effective amount of BCG is about 10^5 to 10^7 cfu per milliliter of tissue culture media and the effective amount of IFN-gamma is about 100 to about 1000 Units per milliliter of tissue culture media.

Bosch et al teach that maturing the immature DCs with **IFN-gamma and BCG** promotes DC production of IL-12, and reduces or inhibits production of IL-10, thereby priming the mature dendritic cells for a type 1 (Th-1) response (para 0039). Bosch et al teach that in contrast to type 1 response, type 2 response is characterized by production of more IL-10 than IL-12 and lack of

induction of a CTL response (para 0022, last two lines). Bosch et al teach that: 1) effective amounts of BCG typically range from about 10.sup.5 to 10.sup.7 cfu per milliliter of tissue culture media, 2) Effective amounts of IFN.gamma typically range from about 100-1000 U per milliliter of tissue culture media (para 0038). Bosch et al teach that Bacillus Calmette-Guerin (BCG) is an avirulent strain of M bovis, and as used herein, BCG refers to whole BCG as well as cell wall constituents, BCG-derived lipoarabidomannans, and other BCG components that are associated with induction of a type 2 immune response (para 0038). Bosch et al teach that BCG is optionally inactivated, such as heat-inactivated BCG, formalin-treated BCG, and the like (para 0038). Thus the type of BCG, and the amount of BCG and interferon gamma are the same as those of the claimed invention. Bosch et al teach that maturation of dendritic cells can be monitored by methods known in the art, such as detection of cell surface markers or cytokine production (p.0041).

Chakraborty et al teach that DCs that produce IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory (abstract, figure 2 on page 93). Chakraborty et al teach that DCs that produce IL-12 up-regulate the co-stimulatory CD80 and CD86 (p.91, second column, first paragraph, table 3 on page 95).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to replace CD40L or LPS taught by Labeur et al with BCG and interferon gamma, as taught by Bosch et al, in the method taught by Labeur et al for maturing DCs for use in producing an anti-cancer response, because of the following reasons:

1) A combination of BCG and interferon gamma selectively produces more maturing DCs that secrete IL-12 than those inhibiting DCs secreting IL-10, as taught by Bosch et al,

2) DCs that secrete IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory, as taught by Chakraborty et al.

3) The ability of DCs to promote antitumor immunity correlates with their high efficiency of stimulating resting T cells and high production of IL-12, as taught by Labeur et al.

In other words, BCG and interferon gamma as maturing agent as taught by Bosch et al would be advantageous, because they selectively enhance the production of stimulating DCs that secrete IL-12, and therefore efficiently stimulating T cells, in view of the teaching of Chakraborty et al, and promoting anti-tumor immunity, in view of the teaching of Labeur et al..

3. Claims 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175.

The following are claims 13-18.

13. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered directly into the tumor.

14. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered into a tumor bed subsequent to surgical removal or resection of the tumor.

15. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered to a tissue area surrounding the tumor.

16. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered into a lymph node directly draining a tumor area.

17. (Original) The method according to claim 1, wherein partially matured dendritic cells are administered directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ.

18. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ.

The teaching of Labeur et al has been set forth above. Labeur et al further teach that **subcutaneous** injection is **not** the optimal cell delivery system for in vitro generated DCs, at least in the mice, because DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice (p.171, second column, last paragraph, bridging p.172, p.174, second column, last paragraph).

Labeur et al do not teach DCs are administered directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to replace s.c. injection of the DCs taught by Labeur et al with administration of said DCs directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, because subcutaneous injection is not the optimal cell delivery system for in vitro generated DCs, at least in the mice, in view that

DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur et al.

4. Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, supra, in view of Nikitina et al, 2001, Int J Cancer, 94: 825-833, IDS# AN of 05/09/07.

Claims 19-20 are as follows:

19. (Original) The method according to claim 1, wherein the partially matured dendritic cells are administered as an adjuvant to radiation therapy, chemotherapy, or combinations thereof.

20. (Original) The method according to claim 19, wherein the partially matured dendritic cells are administered prior to, simultaneous with, or subsequent to radiation therapy, chemotherapy, or combinations thereof.

The teaching of Labeur et al has been set forth above.

Labeur et al do not teach that DCs are administered as an adjuvant to radiation therapy, chemotherapy, or combinations thereof. Labeur et al do not teach that the partially matured dendritic cells are administered prior to, simultaneous with, or subsequent to radiation therapy, chemotherapy, or combinations thereof.

Nikitina et al teach that gamma **irradiation** induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response (abstract, p.831, second column, last paragraph bridging p.382).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration taught by Labeur et al with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina et al.

5. Claims 21-23, 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Sukhatme et al (US 6,797,488), and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claims 6-9 above, and further in view of Sukhatme et al (US 6,797,488).

Claims 21-23, 27-32 are as follows:

21. (Original) A composition comprising dendritic cells partially matured in vitro in the presence of a dendritic cell maturation agent combined with a pharmaceutically acceptable carrier for in vivo administration.

22. (Original) The composition according to claim 21, wherein the partially mature dendritic cells demonstrate an up-regulation of co-stimulatory molecules CD80, CD86 and/or CD54 and retain the ability to uptake and process antigen.

23. (Original) The composition according to claim 21, wherein the composition comprises about 10^2 to about 10^{10} partially matured dendritic cells.

27. (Original) The composition according to claim 21, wherein the partially matured dendritic cells are administered directly into the tumor.

28. (Original) The composition according to claim 21, wherein the partially matured dendritic cells are administered into a tumor bed subsequent to surgical removal or resection of the tumor.

29. (Original) The composition according to claim 21, wherein the partially matured dendritic cells are administered to an tissue area surrounding the tumor.

30. (Original) The composition according to claim 21, wherein the partially matured dendritic cells are administered into a lymph node directly draining a tumor area.

31. (Original) The composition according to claim 21, wherein partially matured dendritic cells are administered directly to a circulatory vessel duct that delivers blood or lymph to the tumor, tumor bed, or a tumor afflicted organ.

32. (Currently amended) The composition according to claim 21, wherein the partially matured dendritic cells are administered into the circulatory system such that the cells are delivered to the tumor, tumor bed, or tumor afflicted organ.

Claims 21, 27-32 recite the claimed composition for administering: 1) in vivo, directly into the tumor, 2) into a tumor bed subsequent to surgical removal or resection of the tumor, 3) to an tissue area surrounding the tumor, 4) into a lymph node directly draining a tumor area, 4) to a circulatory vessel duct that delivers blood or lymph to the tumor, tumor bed, or a tumor afflicted organ, or 5) into the circulatory system such that the cells are delivered to the tumor, tumor bed, or tumor afflicted organ. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims 21,

27-32 read on the ingredient per se, which is a composition comprising dendritic cells partially matured in vitro.

Triozzi et al teach that DCs generated in vitro by GM-CSF and IL-4 express the co-stimulatory molecules **CD80 and CD86**, and a low number of CD83 (p.2649, first column, item under Results). Triozzi et al teach that the amount of DCs generated is from 8.0×10^7 to 18×10^7 (p.2649, first column, item under Results). The amount of DCs taught by Triozzi et al is within the range of the claimed amount of DCs, as claimed in claim 23.

Triozzi et al do not teach DCs in a pharmaceutically acceptable carrier.

Sukhatme et al (US 6,797,488) teach an anti-angiogenic protein, fusion protein thereof (column 2, item under Summary of the invention, bridging column 3), and a composition thereof, wherein the protein is combined with a **pharmaceutically acceptable carrier** (column 16, last paragraph, bridging column 17).

The DCs generated by GM-CSF and IL-4 taught by Triozzi et al would retain the ability to uptake and process antigen, as evidenced by Labeur et al. Labeur et al teach that DCs generated from GM-CSF and IL-4, with or without the addition of TNF-alpha, exhibit intermediate ability to present antigen, after being exposed to the antigen (p.8, last paragraph, bridging p.9 and figure 3 on page 9), which is the same as the claimed ability to uptake and process antigen.

Although the Triozzi reference does not explicitly teach that the generated DCs are partially mature, and retain the ability to uptake and process antigen, however, the claimed DCs appear to be the same as the prior art DCs, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order

to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs taught by Triozzi et al with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for their storage.

Alternatively, the teaching of Labeur et al, Bosch et al and Chakraborty et al has been set forth above.

Labeur et al, Bosch et al and Chakraborty et al do not teach a combination of DCs and a pharmaceutically acceptable carrier.

One would have expected that the non-terminally matured DCs taught by the combined art would up-regulate the co-stimulatory molecules CD80 and CD86, because one would have expected that said DCs are those that secrete IL-12, and because up-regulation CD80 and CD80 is the property of DCs that secrete IL-12, as taught by Chakraborty et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs taught by Labeur et al, Bosch et al and Chakraborty et al with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for their storage.

6. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, in view of Sukhatme et al (US 6,797,488), and as evidenced by

Labeur et al, 1999, J Immunol, 162: 168-175, as applied for claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995).

Claim 24. (Original) The composition according to claim 21, wherein the partially matured dendritic cells have been cryopreserved subsequent to partial maturation.

The teaching of Triozzi et al, Sukhatme et al, and Labeur et al has been set forth above.

Triozzi et al, Sukhatme et al, and Labeur et al do not teach cryopreservation of the DCs subsequent to their partial maturation, i.e. after their generation from exposure to GM-CSF and IL-4.

Murphy et al teach **cryopreservation** of DCs (columns 7-8, and Example 7 on columns 16-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al, using the method taught by Murphy et al, for extended use of the generated DCs.

Alternatively, the teaching of Labeur et al, Bosch et al and Chakraborty et al has been set forth above.

Labeur et al, Bosch et al and Chakraborty et al do not teach cryopreservation of the DCs subsequent to their partial maturation, i.e. after their generation.

Murphy et al teach cryopreservation of DCs (columns 7-8, and Example 7 on columns 16-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Labeur et al, Bosch et al and Chakraborty et al, using the method taught by Murphy et al, for extended use of the generated DCs.

7. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, in view of Sukhatme et al (US 6,797,488), and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, as applied for claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995).

Claims 25-26 are as follows:

25. (Original) The composition according to claim 21, wherein the partially matured dendritic cells have been isolated from a patient to whom they are to be administered.

26. (Original) The composition according to claim 21, wherein the partially matured dendritic cells have been HLA matched to an individual to whom they are to be administered.

The teaching of Triozzi et al, Sukhatme et al, and Labeur et al has been set forth above.

Triozzi et al, Sukhatme et al, and Labeur et al do not teach that the generated DCs have been isolated from the individual to be treated or from a healthy individual HLA-matched to the individual to be treated.

Murphy et al teach that DCs can be obtained from prostate **cancer patient to be treated, or from healthy individual with matched HLA** in terms of HLA antigens, because patients previously treated radiation or chemotherapy often are not able to provide sufficient or effecient DCs (column 6, lines 37-57). Murphy et al teach that CD8+ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule (column 2, second paragraph). It is noted that DCs are antigen presenting cells.

It would have been obvious that the DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al have been isolated from the individual to be treated, as suggested by Murphy et al, to avoid unwanted rejection of foreign DCs. It would have been obvious that the DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

Alternatively, the teaching of Labeur et al, Bosch et al and Chakraborty et al has been set forth above.

Labeur et al, Bosch et al and Chakraborty et al do not teach that the generated DCs have been isolated from the individual to be treated or from a healthy individual HLA-matched to the individual to be treated.

Murphy et al teach that DCs can be obtained from prostate cancer patient to be treated, or from healthy individual with matched HLA in terms of HLA antigens, because patients previously treated radiation or chemotherapy often are not able to provide sufficient or effecient DCs (column 6, lines 37-57). Murphy et al teach that CD8+ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule (column 2, second paragraph). It is noted that DCs are antigen presenting cells.

It would have been obvious that the DCs taught by Labeur et al, Bosch et al and Chakraborty et al have been isolated from the individual to be treated, as suggested by Murphy et al, to avoid unwanted rejection of foreign DCs. It would have been obvious that the DCs taught by Labeur et al, Bosch et al and Chakraborty et al have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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